

Endocrine Issues in ART Complications

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ART Results in

**Multiple Follicle Development
® Multiple Corpora Lutea**

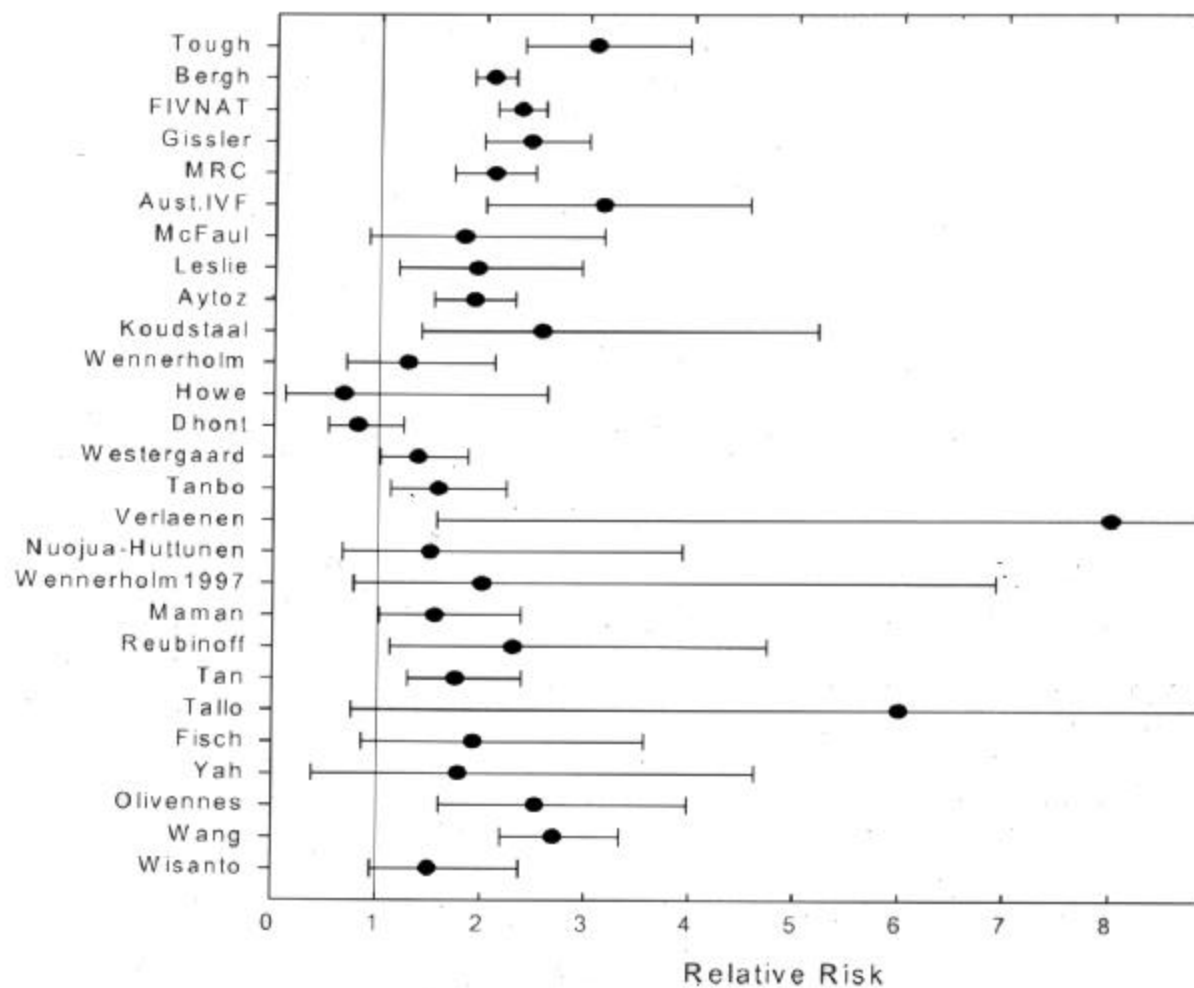
Preterm Birth

ART Results in

Multiple Follicle Development

® Multiple Corpora Lutea ® Preterm Birth

Relative Risk of Singleton Preterm Birth after ART



Singleton Preterm Birth after ART

	<u>ART</u>	<u>Control</u>
Median Incidence n= 27 studies	11.2%	6.0%
Median of Relative Risks	1.93	
	95% CI (1.22 - 3.06)	

Effect of Superovulation upon Preterm Birth

	Insemination	Superovulation + Insemination
Live births		
Total	48	86
Preterm	3	14
%Preterm	6.6%	16.3%

Guzick et al (NCRMN) NEJM 340:177, 1999

Corpus Luteum Products

- **Steroid Hormones**
 Progesterone, Estrogen
- **Peptide Hormones**
 Inhibin
 Relaxin
- **Growth Factors**
 VEGF, FGF, EGF
- **Prostaglandins**

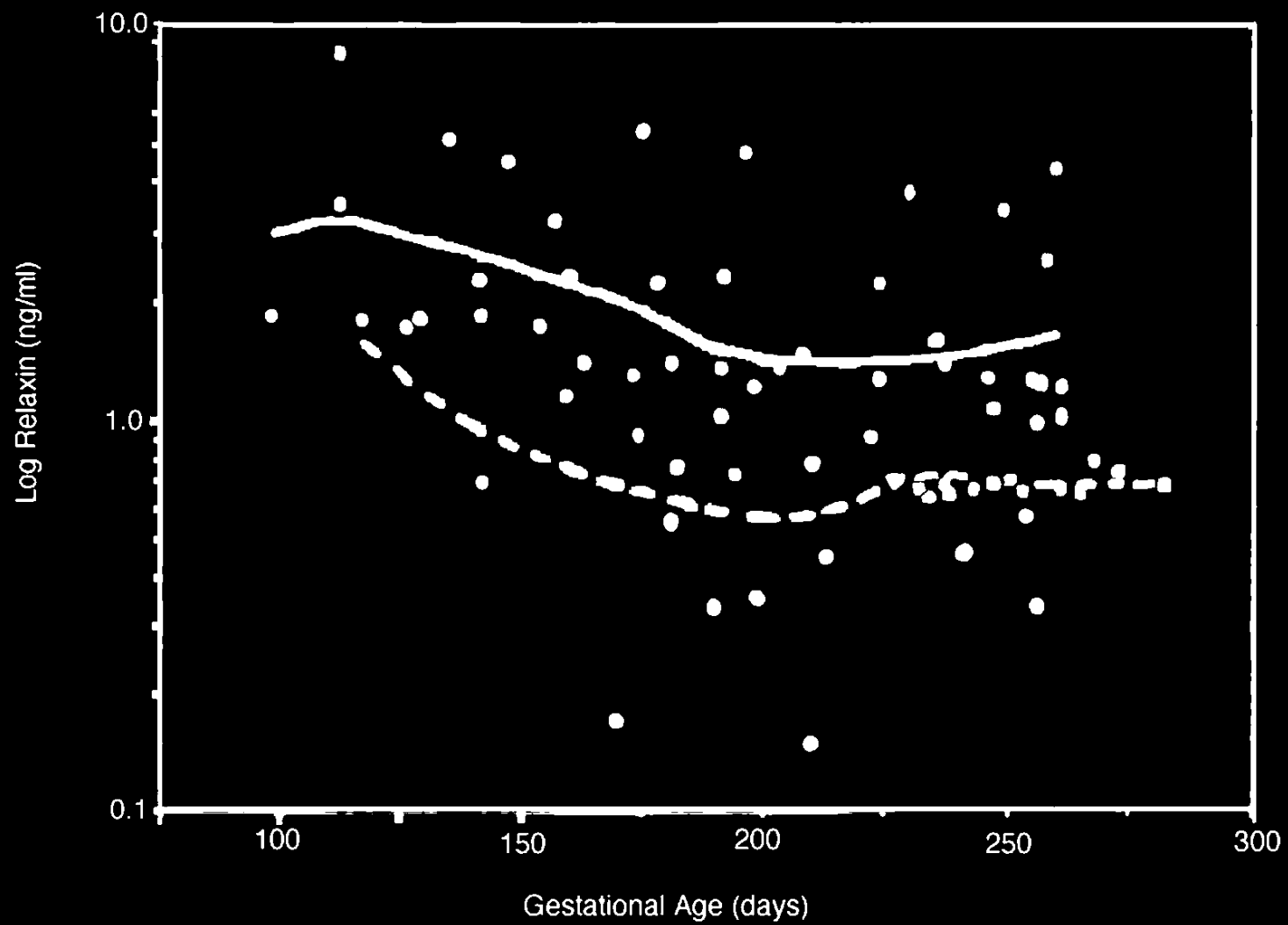
In women,

Relaxin is produced by the corpus luteum, decidua and placenta.

Relaxin is present in maternal circulation throughout the duration of pregnancy.

**Levels of circulating relaxin
are determined by luteal mass.**

Ovulation induction with hMG causes an additional 3.3 fold increase in circulating relaxin.



Hypothesis

Hyperrelaxinemia caused by ovarian stimulation results in an increased rate of premature labor or preterm delivery.

Design

Serum relaxin measured
at 6-12 weeks pregnancy.

Outcome of pregnancy
was determined.

Normal pregnancy group:
38 pregnancies with
mean first trimester levels
of Relaxin = 1.18 ng/ml

3 SD above the mean
= 3.25 ng/ml

Prematurity Risk:

Labor requiring tocolytic therapy before 37 weeks in singletons, before 34 weeks in multiples or cerclage for cervical incompetence.

Preterm Delivery:

Delivery prior to 37 weeks in singletons or 34 weeks in multiples.

Prematurity Risk

Logistic Regression Model

Variable	Estimated Coefficient	Odds Ratio	95% CI for Odds Ratio	p
Relaxin	0.145	2.06 ^{*1}	1.16 - 3.67	0.013
Fetal Number	1.343	3.82 ^{*2}	1.57 - 9.31	0.003

^{*1}odds ratio per 5 ng/ml increase in relaxin

^{*2}odds ratio per unit increases in gestation number

Conclusion

Women who have highly elevated circulating relaxin concentrations in the first trimester of pregnancy are at increased risk of prematurity.

This increased risk is in addition to any increased risk due to increased fetal number.

Relaxin and Preterm Birth

Petersen et al Brit J ObGyn 1992; 99:292

Weiss et al Obstet Gynecol 1993; 82:821

Platek et al Am J Ob Gyn 1997; 176:S54

Vogel et al Am J Ob Gyn 2001; 184:390

**Iams, Goldsmith, Weiss NIH MFM Network
JSGI 2001; 8:39**

Dilatation and ripening of the human cervix involve rearrangement of cervical connective tissue and leukocyte infiltration.

Relaxin has
pronounced effects
upon uterine
connective tissue in
various species
including human.

The maintenance of connective tissue architecture requires a balance between the action of:

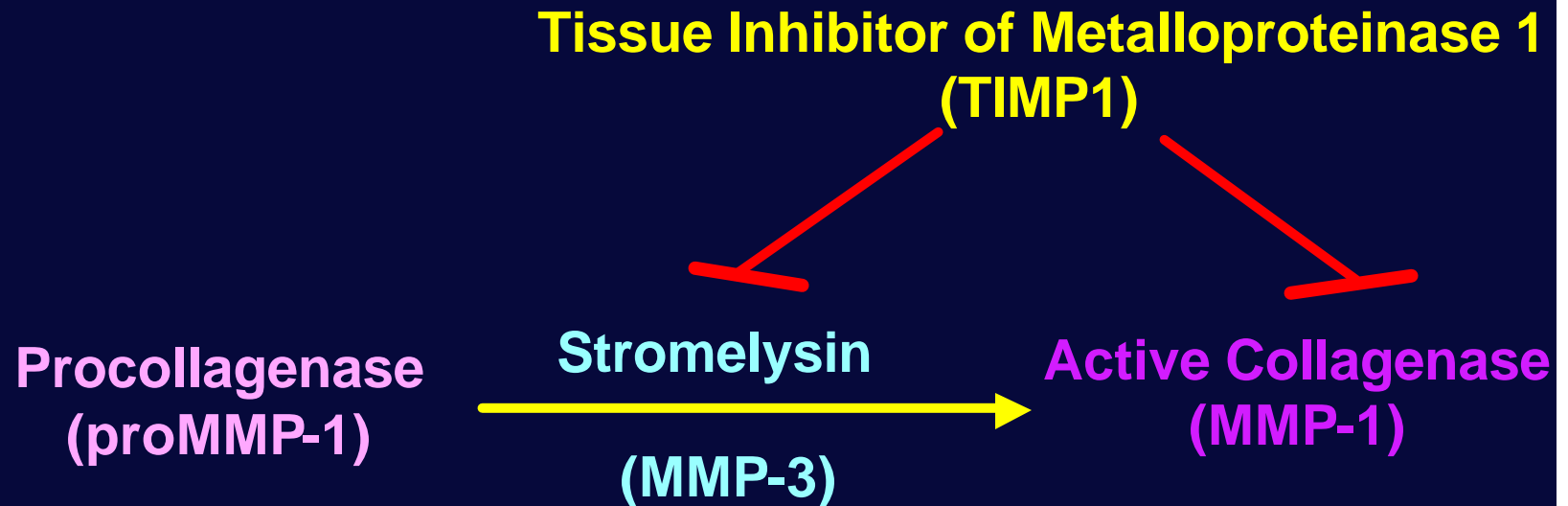
matrix metalloproteinases (MMPs)

degrade the extracellular matrix

tissue inhibitors of MMPs (TIMPs)

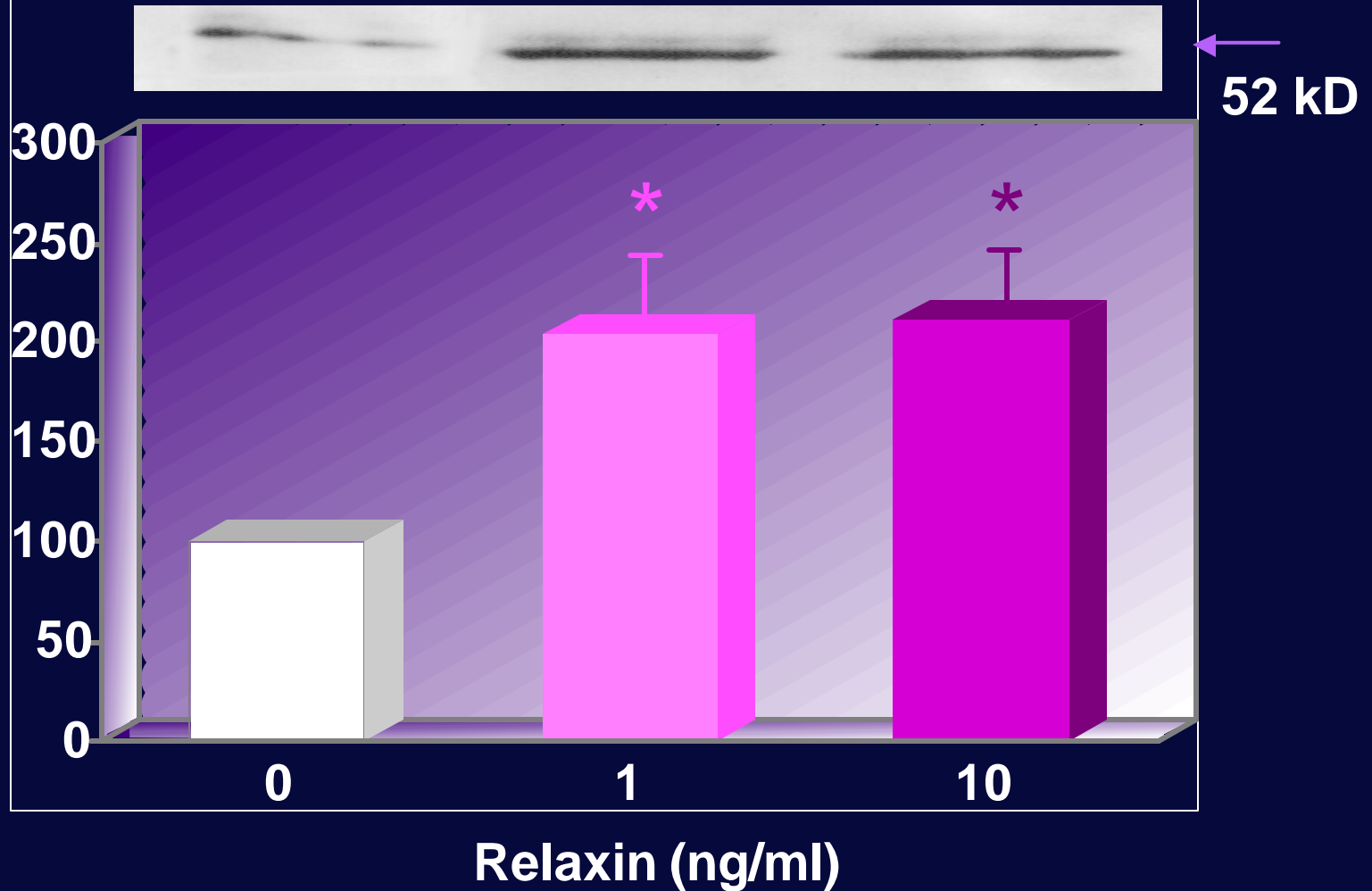
regulate the activity of the MMPs.

Type I Collagen Digestion

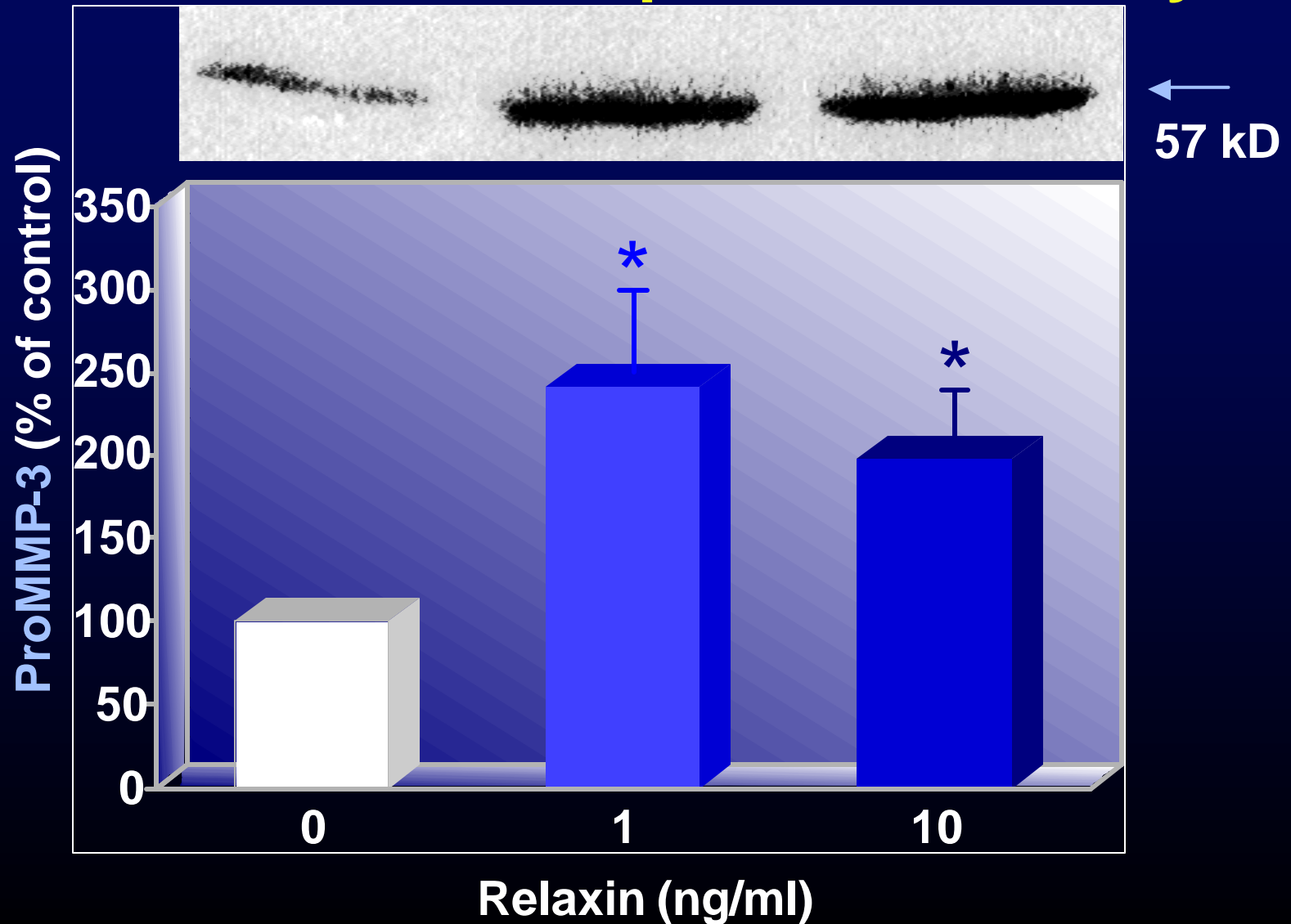


Relaxin's Effect Upon ProCollagenase

ProMMP-1 (% of control)



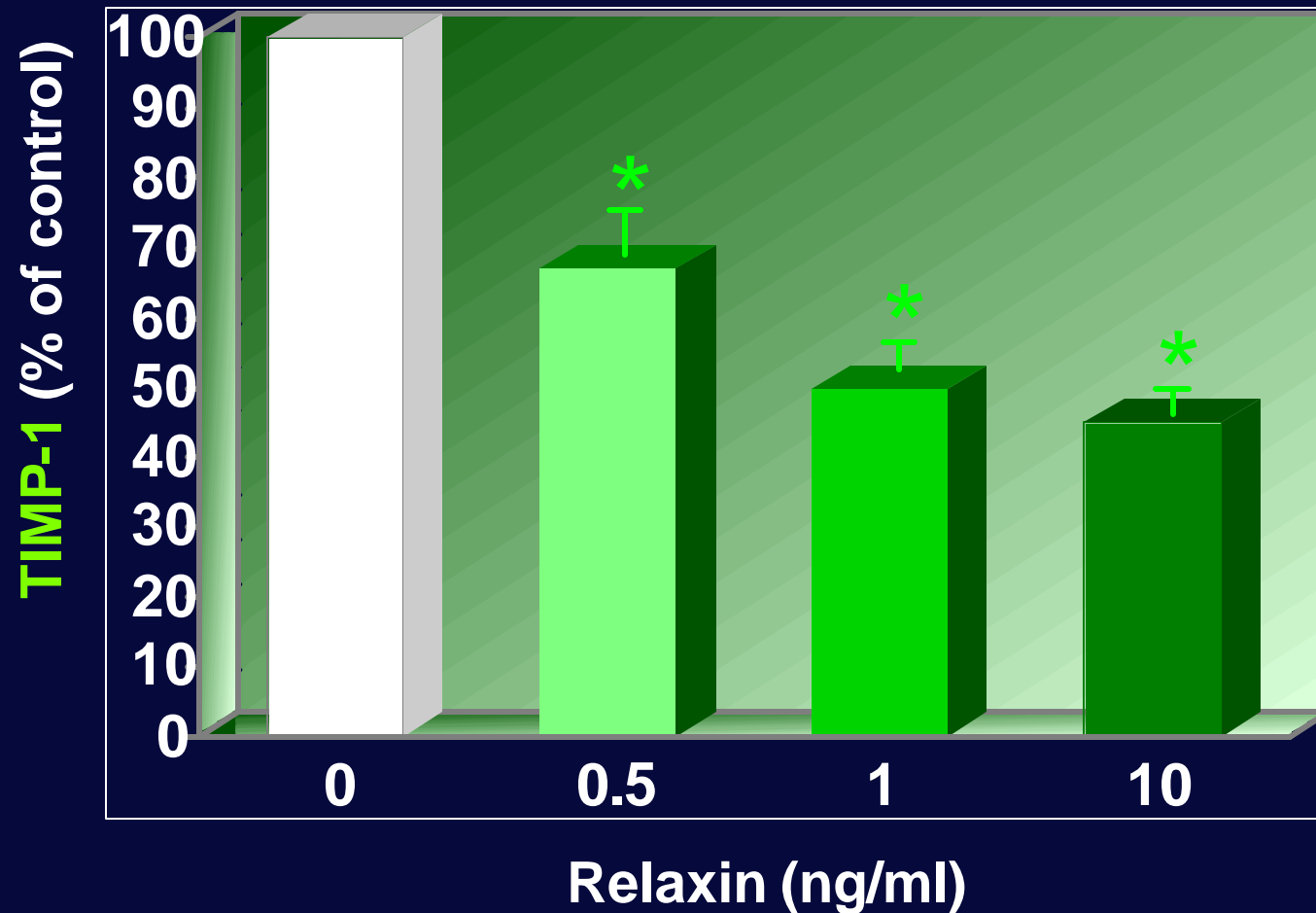
Relaxin's Effect Upon ProStromelysin



Relaxin's Effect Upon TIMP-1



←
28 kD



Relaxin is a positive regulator of matrix metalloproteinases at the level of the cervix.

- Increases expression of collagenase (MMP-1) and stromelysin (MMP-3) and inhibits TIMP-1

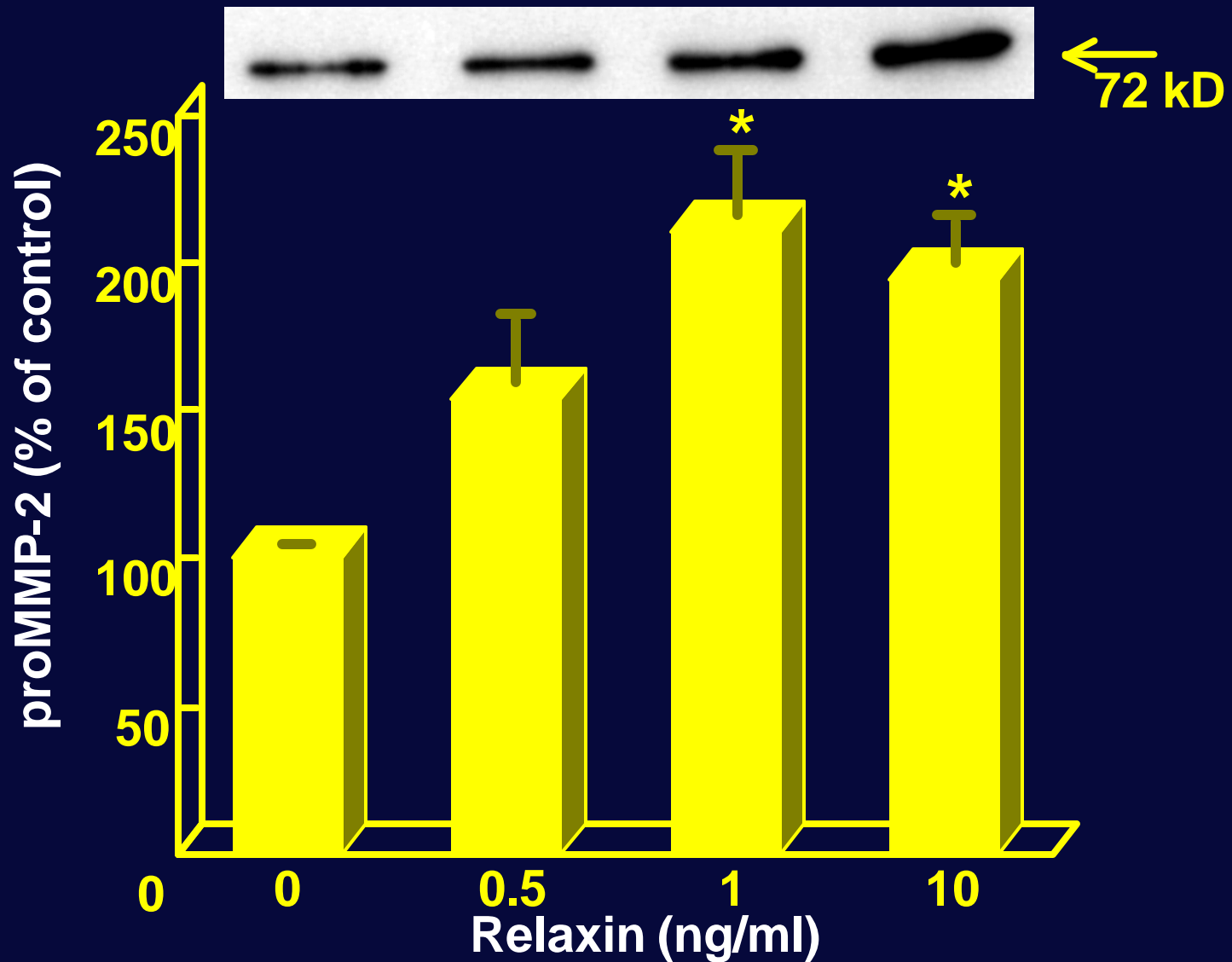
Net effect
increased collagenolytic activity

Type IV Collagen Digestion

Basement Membrane
Blood Vessel Endothelium

Gelatinase A (MMP-2)

Relaxin's Effect Upon ProGelatinase A



Relaxin increases proGelatinase A
(proMMP-2)expression.

Effect - increased leukocyte
infiltration

Progesterone



**Procollagenase
(MMP-1)**

No Effect

**Progelatinase
(MMP-2)**



**Prostromelysin
(MMP-3)**

No Effect

**Tissue Inhibitor
(TIMP-1)**

Relaxin



Relaxin

increases leukocyte infiltration into rhesus monkey endometrium in vivo.

Control (n=43)

101.5 ± 7

Relaxin Treated (n=57)

188 ± 6

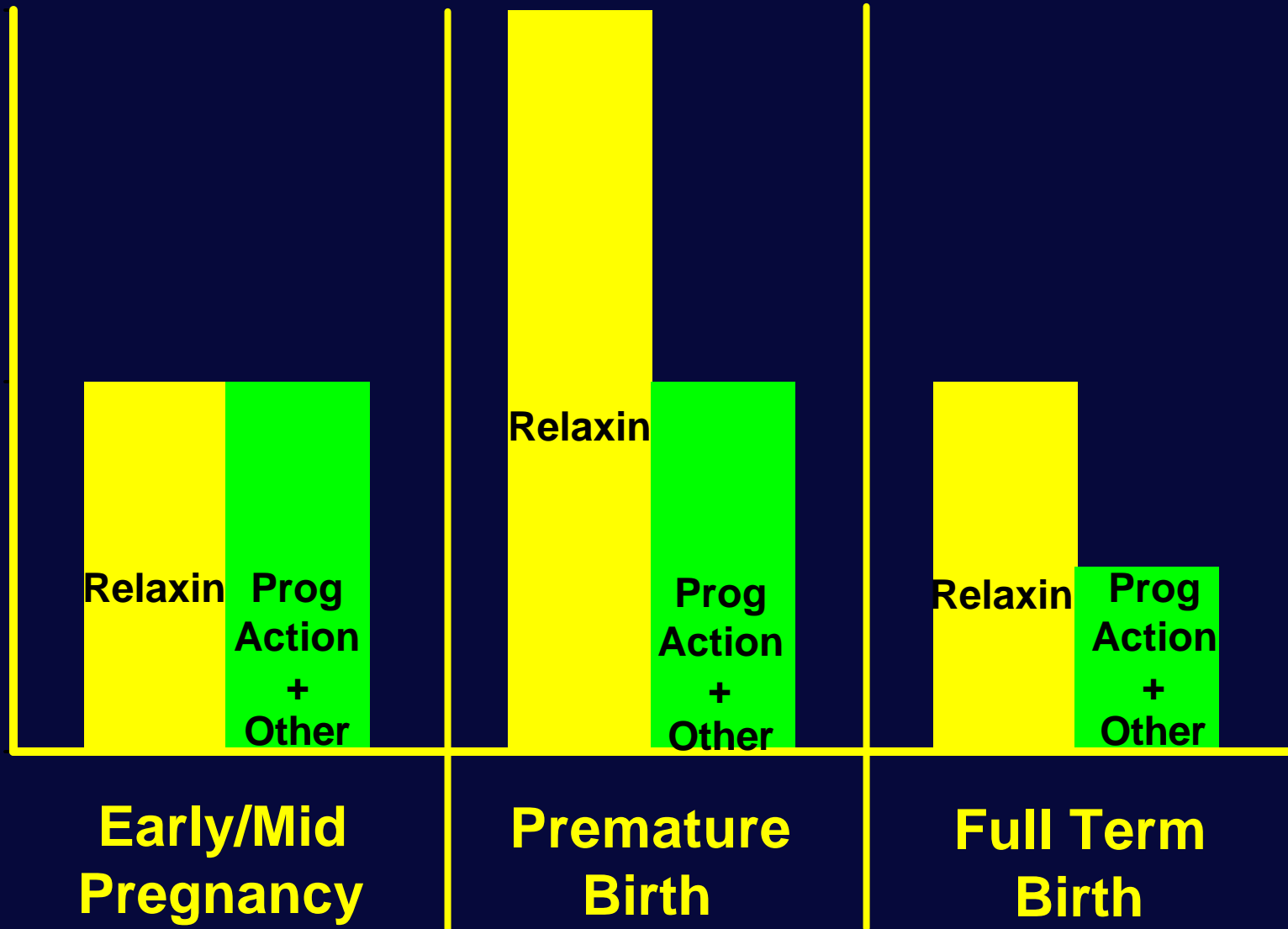
$p=0.0001$

Summary:

Hyperrelaxinemia and Preterm Birth

Relaxin levels are increased in women destined to deliver prematurely.

Relaxin affects the uterus promoting the types of biochemical changes which cause delivery.



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Median Serum Relaxin Levels in Very Preterm, Moderately Preterm and Term Deliveries

	Very preterm (n = 11)	Moderately preterm (n= 42)	Term (n = 123)	
Relaxin (pg/mL)	1088	616	669	P= 0.03
Gestational age (d) at sampling	120	122	121	
Gestational age (d) at delivery	224	253	283	
Birth weight (g)	1750	2700	3530	

Vogel, et al. Am J Obstet Gynecol 184:391, 2001